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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
HUYNH, P	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No. 09/402,636	Applicant(s) MASCAX ET AL.	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *8, 10, 12-16, 19, 23-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 9, 11, 17-18, 20-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. Applicant's election with traverse of Group I, species vitamin D moiety, bisphosphonate moiety, estrogen and antiestrogen in Paper No. 10 is acknowledged. The traversal is on the grounds that the examiner has not provided classification for any of the groups. This is not found persuasive because this application is filed as a **371** of PCT US98/02899 and lacks unity of invention since the subject matters of the five Groups do not contribute a special technical feature when view over the prior art for reason set forth in Paper No. 7 (See MPEP chapter 1800). The requirement is still deemed proper and is therefore made FINAL.

   Claims 1-40 are pending.

   Claims 8, 13-16, 19, 23-40 are withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to non-elected inventions.

   Claims 1-7, 9, 11, 17-18, 20-22 that read on Group I, species Vitamin D moiety conjugated to bisphosphate moiety, estrogen and anti-estrogen are being prosecuted in this Office Action.

2. The drawings, filed 4/26/00, are approved.

3. The declaration is defective. A new declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

   The declaration is defective because:

   The words are **not** legible.

4. This application does not contain an abstract on a separate page of the disclosure as required by 37 CFR 1.72(b). An abstract on a **separate sheet** is required.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

   The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-7, 9, 11, 17-18, 20-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for conjugate comprising one vitamin D moiety associated with bisphosphonate, does not reasonably provide enablement for vitamin D conjugated to estrogen or their equivalents, and antiestrogen to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized in *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The instant claims are drawn to a conjugate of Vitamin D wherein the Vitamin D moiety is linked to a bisphosphonate, estrogens or their equivalents, via an amide linkage at Carbon position 1, 3, 24 and 25. The specification as filed only enabled for 1 α-(OH)-24-aminoalkyl-1, 1-bisphosphonate-D_2 (See page 26), 1-aminoalkyl-1, 1-bisphosphonate-D_2 (see page 27), 1α, 24-$(OH)_2$-3-aminoalkyl-1, 1-bisphosphonate-D_2 (See page 29), 1-α-aminoalkyl-1, 1-bisphosphonate-25 (OH)-D_3 (see page 30), 1α, 25-$(OH)_2$-3-aminoalkyl-1, 1-bisphosphonate-D_3 (See page 32) and 1α-(OH), 25-aminoalkyl-1, 1-bisphosphonate-D_3, (See page 32). However, the specification disclosure is insufficient to enable one skilled in the art to practice the invention with any vitamin D conjugates as broadly as claimed without an undue amount of experimentation. There is insufficient working examples and guidance in the specification regarding to **the estrogen or their estrogen equivalent**, anti-estrogens to be conjugated to the vitamin D molecule. There is insufficient biochemical information regarding to the chemical reaction, the condition to which the reaction will take place, the functional group within the estrogen, antiestrogen and estrogen equivalent structure may be suitable for linking to Vitamin D, the **specific estrogen or their estrogen equivalent** commensurate with the scope of the claims. Therefore predicting which estrogen or anti-estrogen will conjugate with vitamin D under unspecified condition, with the exception of bisphosphonate, is complex and undue amount of experimentation. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Regarding to a pharmaceutical composition as recited in claim 20-22, the specification as filed fails to provide any *in vivo* data, working examples, and guidance with respect to therapeutic effective dosages of the conjugates to treat any condition.

A "pharmaceutical composition" in the absence of *in vivo* data are unpredictable for the following reasons: (1) the conjugate may be inactivated before producing an effect due to proteolytic degradation; (2) the conjugate may be inactivated before producing an effect due to metabolic clearance; (3) the conjugate may be inactivated before producing an effect due to the inherently short half-life of the conjugate (bioavailability); (4) the conjugate may not reach the target area because, i.e. the conjugate may be adsorbed by fluids, cells and tissues where the conjugate has no effect; and (5) other functional properties, known or unknown, may make the conjugate unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In view of the quantity of experimentation necessary, the absence of supporting evidence for in vivo treatment for any disease, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

7. Claims 1-7, 9, 11, 17-18, 20-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The instant claims 1-7, 9, 11, 17-18, 20-22 are drawn to "a Vitamin D conjugate to a therapeutic agent wherein the therapeutic agent is selected from the group consisting of estrogens or their equivalents, antiestrogen". In the instant case, the specification does not convey to the artisan that the applicant had possession, at the time of invention, of the claimed Vitamin D conjugated to estrogen, estrogen equivalent, or antiestrogen other than Vitamin D conjugated to bisphosphonate. Since only six Vitamin D conjugates are provided and all conjugated to bisphosphonate, any Vitamin D conjugated to estrogens or their equivalents, and vitamin D conjugated to antiestrogen are not adequately described. One of skill in the art would therefore conclude that the specification fails to disclose a representative number of species to describe the claimed genus. See *Eli Lilly*, 119F.3d 1559, 43 USPQ2d 1398. Due to the broad claims, none of

these conjugates (with the exception of Vitamin D conjugated to bisphosphonate) meets the written description provision of 35 USC 112, first paragraph. In re Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See Vas-Cath, page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath, page 1116.) The skilled artisan cannot envision all the contemplated Vitamin D conjugate **to estrogens or their equivalents** and therefore conception cannot be achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

Therefore, only the conjugates of Vitamin D to bisphosphonate identified in the specification on page 26, 27, 29, 30, 32 and 33, meets the written description provision of 35 USC 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.) Applicants are directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, & 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1, 17-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "**estrogens or their equivalents**" as recited in claim 18 is indefinite because the claim as written reads on every compound that has estrogen like activity, including phytoestrogen and estrogen from any source. In addition, the phrase has no support in the specification as filed.

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

11. Claims 1, 3-4, 7, and 20-22 are rejected under 35 U.S.C. 102(e) as being anticipated by Knutson *et al* (US Pat No. 5,602,116, Feb 1997; PTO 892).

Knutson *et al* teach a conjugate comprising at least one vitamin D moiety associated with a target molecule moiety having an affinity for a tissue of interest wherein the target molecule is estrogens or equivalent, bisphosphonate, metal ion such as calcium, cobalamin, pertussis toxin, boron (See entire document, column 13 and Table 1 in particular) and a pharmaceutical composition comprising a differentially degradable coating for time release wherein said coating is an enteric coating (See Column 6 line 8-50, in particular). The connecting group is a bond between the vitamin D moiety and the target molecule (See claim 1, in particular).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced vitamin D conjugates.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1-7, 9, 11, 17-18 and 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knutson *et al* (US Pat No. 5,602,116, Feb 1997; PTO 892) and Kobayashi *et al* (Anal Biochem 244(2): 374-83, Jan 1997; PTO 892) in view of Bauss et al (Calcif Tissue Int 59(3): 168-73, Sept 1996; PTO 892).

Knutson *et al* teach a conjugate comprising at least one vitamin D moiety associated with a target molecule moiety having an affinity for a tissue of interest has been discussed supra.

Knutson differ from the claimed invention by not using a bifunctional connector between the target molecule bisphosphonate and the vitamin D moiety.

Kobayashi *et al* teach a conjugate comprising at least one vitamin D associated with a target molecule moiety having an affinity for a tissue of interest in a 1:1 molar ratio wherein the vitamin D is associated with the target molecule via a connecting group having a bond therebetween them encompassed instant claims 1-4 (See entire document). The said connecting group is a bifunctional connector and the vitamin D moiety is associated with at least one additional connecting group as encompassed by claims 5-6 (See Fig 1, in particular). The conjugate is linked to said vitamin D moiety via an amide linkage, a biotin-avidin linkage (See entire document, abstract and page 381 right column, in particular).

Bauss *et al* teach a conjugate comprising at least one target molecule moiety wherein the target molecule is a bisphosphonate moiety associated with at least one one-therapeutic agent wherein said therapeutic agent is estrogens or their equivalents encompassed by claims 1, 17 and 18 (See entire document). The said conjugate is associated with a connecting group forming a bond between them and said connecting group is a bifunctional connector as encompassed by instant claims 2-6 (See entire document, Fig 1 in particular).

Therefore, it is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for

very same purpose; idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06. One having ordinary skill in the art at the time the invention was made would have been motivated with a reasonable expectation of success to combine vitamin D-bisphosphonate conjugate and estrogen or estrogen equivalent-bisphosphonate as a method of treating bone because bisphosphonate conjugates have been shown to have high affinity for bone without the drawback of systemic effects of the steroids and the added benefit of not having the development of hypercalcemia induced by vitamin D as taught by Bauss et al (page 168, right column second paragraph, and page 171, in particular).

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

17. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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